

Development and Consideration of Global Policies for Managing the Future Risks of Poliovirus Outbreaks: Insights and Lessons Learned Through Modeling

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The success of the Global Polio Eradication Initiative promises to bring large benefits, including sustained improvements in quality of life (i.e., cases of paralytic disease and deaths avoided) and costs saved from cessation of vaccination. Obtaining and maintaining these benefits requires that policymakers manage the transition from the current massive use of oral poliovirus vaccine (OPV) to a world without OPV and free of the risks of potential future reintroductions of live polioviruses. This article describes the analytical journey that began in 2001 with a retrospective case study on polio risk management and led to development of dynamic integrated risk, economic, and decision analysis tools to inform global policies for managing the risks of polio. This analytical journey has provided several key insights and lessons learned that will be useful to future analysts involved in similar complex decision-making processes.

KEY WORDS: Decision analysis; dynamic disease model; outbreak; polio eradication; process; risk analysis; uncertainty; variability

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1. INTRODUCTION

“All decisions are based on models . . . and all models are wrong.”

John Sberman⁽¹⁾

“All models are wrong but some are useful.”

George Box⁽²⁾

In theory, modeling provides the opportunity to analyze decision options systematically, which allows explicit consideration of the possible alternatives. For complex problems, models can help provide a shared vision of the system, show the different components and how they interact, and synthesize the existing information.⁽³⁾ Models can also offer insights about important sources of variability (i.e., real differences between individuals that matter in the context of the decision) and uncertainty (i.e., imperfect information) and their implications.⁽⁴⁾ Thus, models can theoretically help decisionmakers choose

more wisely. But how much do models really help in practice?

Behind any model lies a story about the analysts and process that created it, yet descriptions of this background rarely find their way into the literature. Unfortunately, this often means that analysts do not benefit from valuable process lessons learned by others, and strategies that might help reduce the amount of “muddling through” remain undocumented. This article seeks to tell the story of five years of our experience developing a decision analytic modeling tool to support global policies for managing the risks of polio after eradication. We summarize the interplay of key factors involved in polio risk management and offer perspectives on the evolution of the project structured according to the five requirements that we believe drove its early success.

2. CONTEXT

A retrospective analysis of the history of polio vaccination in the U.S. documents the incredible story of this successful public health intervention,⁽⁵⁾ starting from a peak of over 21,000 cases of paralytic polio in 1952 to no wild poliovirus cases in the United State since 1979 and only rare importation-associated cases since then. On April 12, 1955, researchers demonstrated the effectiveness of the Salk polio vaccine in the largest U.S. clinical trial ever conducted,⁽⁷⁾ and the news media that day exclaimed exciting themes: “The vaccine works.” “It is safe, effective and potent.” “Polio is conquered.” The promise of a vaccine that would end the fear caused by polio brought hope and led to long lines of people seeking vaccination. The United State began vaccination in 1955 with the Salk inactivated poliovirus vaccine (IPV), but switched in the early 1960s to the Sabin oral poliovirus vaccine (OPV) due to its relatively lower cost, easier administration, and ability to provide more effective population immunity.⁽⁸⁾ By the early 1990s, the Americas succeeded in eliminating wild polioviruses^(9,10) and vaccine-associated paralytic polio (VAPP) was the only remaining cause of paralytic polio in the United State (i.e., less than 10 cases per year with an annual birth cohort of approximately 4 million children).⁽¹¹⁾ Consequently, in the late 1990s the United State returned to use of IPV enhanced-potency with (eIPV) at a relatively high cost to avoid the small but significant burden of VAPP that occurs at low rates with OPV.⁽¹²⁾ The availability of the eIPV option, progress toward global polio eradication and decreased risk of wild poliovirus importation into the United State, and

concern about the perception of risks of vaccination exceeding the benefits weighed in favor of the shift to eIPV for routine vaccination in the United States. Other developed countries that used OPV similarly moved toward eIPV use. However, the Global Polio Eradication Initiative (GPEI) and most of the countries in the world continue to rely on OPV, the vaccine of choice because it can more effectively interrupt transmission in endemic areas and provides greater population or herd immunity. OPV is also less costly and easier to administer than IPV.

In 1988, with an estimated 350,000 annual cases of paralytic polio globally, the World Health Assembly committed to global eradication of polio.⁽¹³⁾ By 2003, endemic circulation of wild polioviruses continued in only six countries (Nigeria, Niger, Egypt, India, Pakistan, and Afghanistan), but new challenges (political and logistical) led to outbreaks, exportations, and reintroductions of polio in a number of previously polio-free African and Asian countries with outbreaks in 2002–2005.⁽¹⁴⁾ These reintroductions and outbreaks demonstrated the ability of polioviruses to rapidly spread globally and reinfect polio-free countries that stopped their intensive eradication activities. Thus, maintaining vigilance in sustaining vaccination and surveillance remains essential, at least until the successful global eradication of all wild polioviruses.

As the world made progress toward global polio eradication, many questions emerged and world leaders faced and continue to face a broad range of decisions with complex implications. For example, while the World Health Assembly leaders who committed to eradication in 1988 expected that successful eradication would mean complete cessation of polio vaccination (as occurred following the eradication of smallpox), current perceptions by some countries about the risks of bioterrorism and use of IPV for routine vaccination lead to the logical question of whether developed countries will ever stop using IPV. For countries now using OPV, the complicated set of options includes switching to IPV (at high cost and presumably at the expense of investing in other public health measures), continuing to use OPV, or stopping vaccination.⁽¹⁵⁾ Continuing to use OPV emerges as problematic for at least two reasons: (1) OPV use leads to a small, but finite and reasonably predictable number of cases of VAPP, and (2) circulation of OPV vaccine-derived polioviruses (cVDPV) in countries with low coverage with OPV has resulted in several outbreaks (due to the OPV viruses reverting to a neurovirulent form).⁽¹⁶⁾ The possibility of cVDPVs means

that low levels of OPV coverage present a significant risk, and that continued use of OPV should involve efforts to maintain very high coverage, most likely in the form of the supplemental immunization activities now used in the GPEI (i.e., National Immunization Days). The risks for outbreaks after eradication range from the potential for cVDPVs, potential breaches in containment of transmissible viruses in laboratories or IPV production facilities, intentional reintroduction, and the possibility of vaccine virus reversion to neurovirulence from rare instances of immunocompromised individuals who excrete polioviruses for prolonged time periods after they received OPV (immunocompromised VDPVs or iVDPVs).⁽¹⁷⁾ Clearly, even small risks may represent important concerns when considering the impact of reintroduction of polioviruses as the population susceptibility increases.

As national and world health leaders considered various options for the “end-game” of polio eradication, they recognized that the opportunity to stop OPV vaccination necessitates development of a strategy (i.e., response plan) and the tools (i.e., vaccine stockpile and/or ongoing production) for responding to a future outbreak. They also remain interested in understanding the risks, costs, and benefits of the various options. With the success of national eradication programs and the elimination of disease burden, decisionmakers may tend to divert resources away from polio risk management and toward other more pressing and visible priorities. However, this may not represent the best strategy if it jeopardizes sustained achievement of eradication or places their country at a higher risk in the long-term.

Modeling can provide an opportunity to explore these tradeoffs. The authors worked in a collaborative partnership to identify and address these key questions regarding polio risk management. Over the course of this work, we identified several requirements that allowed us to contribute to the development of international public health policies, and we believe that these lessons learned have broader application.

2.1. Requirement 1: Establish a Shared Vision to Guide Collaboration

“Genius is one percent inspiration and ninety-nine percent perspiration.”

Thomas Edison

“The beginning is the most important part of the work.”

Plato

This collaboration involves many partners that each brought very different experiences, perspectives, and resources to the team. In 1988 the GPEI launched with the mission of eradicating wild poliovirus globally and under the leadership of four spearheading partners: the World Health Organization (WHO), the U.S. Centers for Disease Control and Prevention (CDC), United Nations Children’s Fund (UNICEF), and Rotary International. These partners remain committed to achieving global eradication. The large extended team associated with the GPEI includes leading experts on all aspects of polio disease and its control. At the time this collaboration started, however, the GPEI extended team included relatively few individuals trained as economists or decision analysts.

In contrast, the first two authors started with limited expertise on polio. In 1998, the lead author began working with a doctoral student to review and assess the published, peer-reviewed pediatric cost-effectiveness and cost-benefit analyses literature. That review yielded several key insights, including the preponderance of analyses for vaccine interventions, little recognition of variability and uncertainty, little consideration of changes over time, and a lack of dynamic disease modeling for modeling outbreaks^(3,18) in the context of assessing the benefits of vaccines. Thus, in 2001, the first two authors began working on a retrospective cost-effectiveness analysis that sought to demonstrate the importance of considering time and using a dynamic disease model in cost-effectiveness analyses. They selected polio as a case study because it offered a long history (but not too long) and they recognized that the approaching eradication of wild poliovirus meant that this would be a good time to reflect on the aggregate benefits of historical interventions.

Throughout most of 2001, the first two authors reviewed the literature on polio and built a model to perform a first-cut retrospective cost-effectiveness analysis for polio interventions. Fig. 1 shows the first draft of the model results demonstrating the importance of using a dynamic model to capture the population immunity benefits of OPV. The lines in the figure compare the expected number of annual paralytic cases over time in the absence of vaccination, with vaccination using a static model (i.e., a model in which only the vaccine recipient derives benefits from the vaccine), and with vaccination using a dynamic model (i.e., a model that appropriately captures the effect of population immunity). In the process of reviewing the literature and building this model, the first two authors contacted a number of

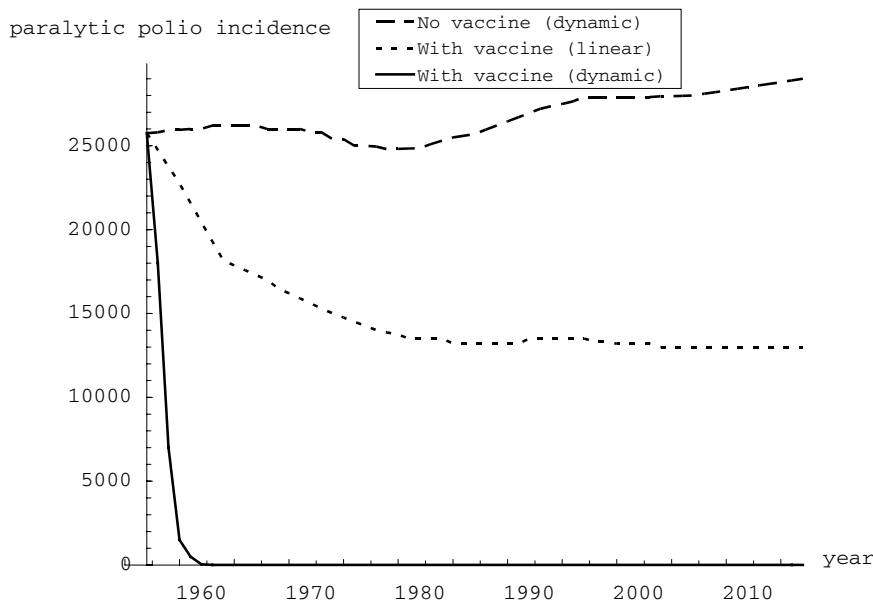


Fig. 1. First results from our retrospective SIR transmission model, presented at the CDC in December 2001, showing paralytic polio incidence without vaccine (dynamic), with vaccine static, and with vaccine dynamic.

polio experts, including leaders at the CDC. In addition, the lead author collaborated with another vaccine economics researcher at Harvard to develop the Harvard-CDC Joint Initiative on Vaccine Economics (JIVE) project, which created a mechanism for developing research collaborations with the CDC. After presenting the retrospective model and insights to the CDC's Global Immunization Division and Polio Eradication Branch, the first two authors hoped that this meeting would yield better data and information about some of the big uncertainties remaining in the model at that point. This discussion led to much more than just better data. At the end of that presentation several of the authors (SLC, RWS, HJ, and VMC) immediately recognized and appreciated the opportunity that this type of model offered in evaluating prospective decisions. Over the next several months a shared vision and overall project framework evolved. Because of the complexity of polio risk management, it became clear that the best possible model about the risks, costs, and benefits of various strategies required integrated policy modeling and an ongoing strong collaboration between modelers and those with programmatic and scientific expertise.

The larger collaboration described in this article really began at that meeting. Thus, the work that the first two authors performed independently established credibility with the polio experts and identified opportunities for using these types of analytical tools to confront global polio risk management. It was not just being in the right place at the right time but an up-

front investment and hard work that laid the groundwork for the effective collaboration. In addition, the receptiveness of the polio experts to discuss initial questions raised by the first two authors, engage in conversations about the future, and commit time and resources to a process of building a decision model represented essential first steps.

2.2. Requirement 2: Survey, Understand, and Establish a Close Network with the Experts and the Larger Community of Stakeholders

"If a man will begin in certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties."

Francis Bacon

"Medicine is the science of uncertainty and an art of probability."

Emily Mumford

The collaboration launched with the concept of developing a simple decision analytic model to assess the risks, costs, and benefits of the five main policy options under discussion at the time. Although various members of the team initially expressed different expectations for complexity in the modeling effort, as the group discussed simplifying assumptions it quickly became clear that the model would need to deal with many complexities by characterizing them quantitatively to the extent possible. Fig. 2 shows a picture of the initial working model, which remarkably fit onto

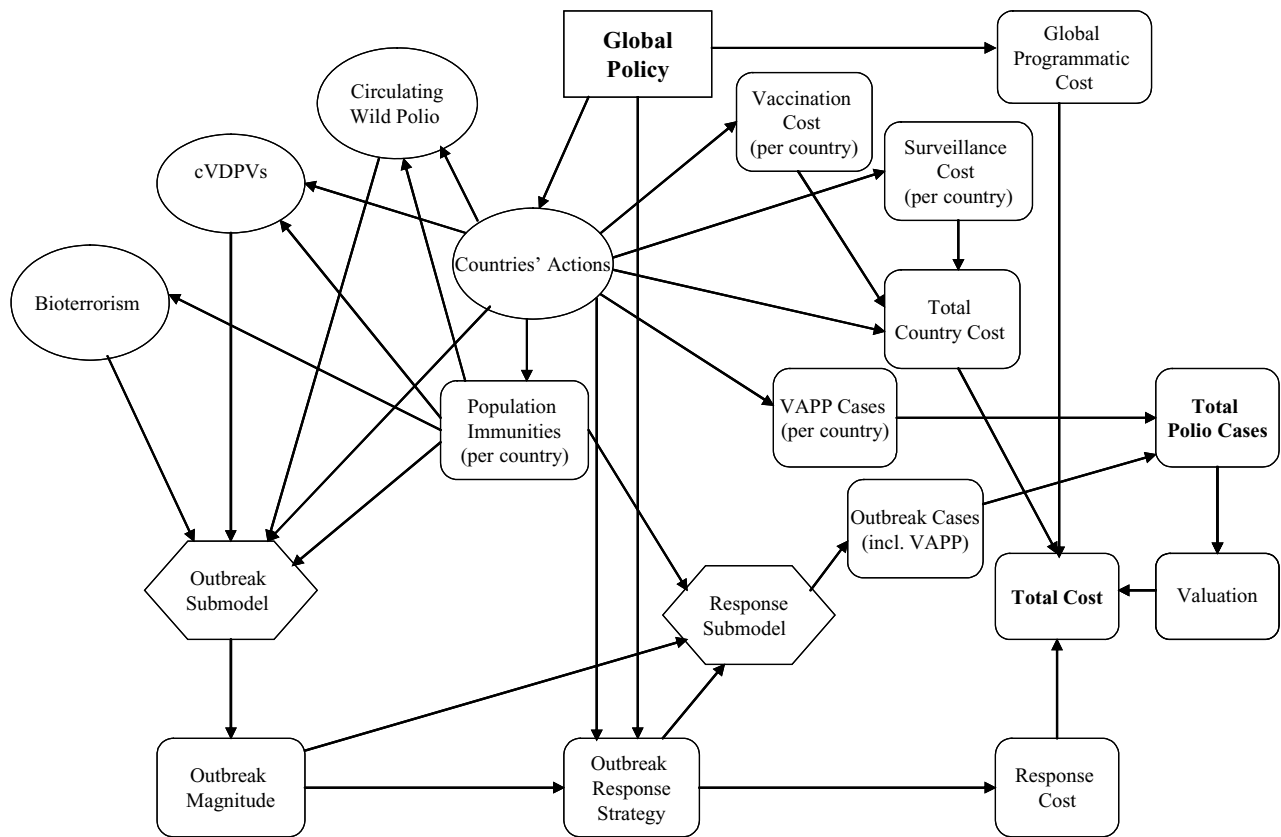


Fig. 2. Initial influence diagram of the polio decision model (the rectangular box represents a decision node, the diamonds represent sub-models, the ovals random events, and the rounded rectangles intermediate variables or outcomes).

a single page. However, some stakeholders preferred more simple representations of the model so the team relied on the model schematic shown in Fig. 3 for presentations.

The collaborators benefited enormously from the process of asking and answering critical framing questions, and from knowledge sharing by the po-

lio experts who knew the data extremely well and who could readily identify the relevant pieces of information. One of the initial challenges for the collaboration came from prior attempts by the polio experts to collaborate with economists and the inability to span the gap. Thus, although the collaboration benefited from enthusiasm and strong support from all of its participants, this does not mean that every stakeholder appreciated its potential value. For example, in the context of already scarce resources, some stakeholders argued that an effort focused on posteradication planning did not represent a priority in the face of competing priorities for resources and the real challenges faced in achieving polio eradication itself. In our efforts to promote the value of this effort, we emphasized the value of the process in addition to the final products. In 1988, the World Health Assembly committed to the eradication of polio by the year 2000 with a defined set of strategies, but without quantitative estimates of the human or financial resources required.⁽¹⁹⁾ We emphasized that a dynamic, decision

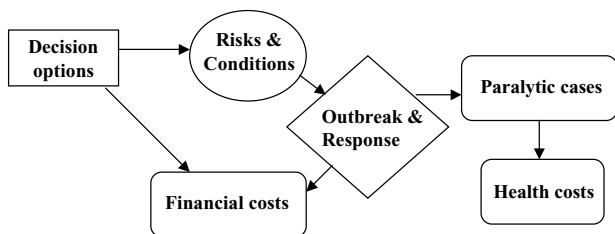


Fig. 3. Simplified diagram of model components (the rectangular box represents a decision node, the diamonds represent sub-models, the ovals random events, and the rounded rectangles intermediate variables or outcomes).

analytical model could give decisionmakers good information about the risks, costs, and benefits of different options. Providing this information at the right time, however, would require investing up front in active collaboration to build the model.

We also recognized the many audiences for the model. Thus, while we wanted the model to remain as simple as possible, we also expected to develop the model in the context of discussions in which some of the participants might express different preferences. We understood that the information and priorities might change and that our model needed to remain flexible to accommodate these changes. This made it essential for us to be adaptive, clear about what others could expect from us, and clear that the process would take time. Our collaboration focused on process, and we emphasized the value in the process of developing the model, particularly in clarifying the key issues and sorting through the options with the best available information.^(3,20) We worked to emphasize that our collaboration offered a rigorous process and tools that would provide defensible insights to help others evaluate the options and make more informed choices, instead of focusing on providing a model with “the” answer. Since we did not develop the model instantly or produce immediate results and since decisionmakers faced the immediate priority of eradicating wild poliovirus, some of the collaborators needed to continually promote the project. Thus, it remained necessary to convince some policymakers appropriately focused on the urgency of eradicating the disease to also consider the value of and need to devote time and resources to posteradication planning. The process of systematically compiling all decision options (an initial deliverable) helped to demonstrate the number and complexity of decisions the program needed to make, many of which required investments and planning in the critical time window prior to eradication. For example, establishment of an OPV stockpile and licensure of monovalent OPV vaccines would become very difficult in a posteradication era with no massive OPV production and no imminent need to eradicate remaining wild poliovirus serotypes.

2.3. Requirement 3: Effective Communication and Built-In Capacity to Adapt and Respond to Changes in the Program or System

“I was taught that the way of progress is neither swift nor easy.”

Marie Curie

“Remember that time is money.”

Benjamin Franklin

The enthusiasm about the model within the group of collaborators at CDC helped tremendously in our efforts to collect and synthesize information. One of the most unique aspects of the CDC polio team came from the impressive collaboration between the lab and program scientists. Even though the laboratory lies within one division of the CDC and the program in another, over a decade ago, the leaders of these two groups started a tradition of meeting on Friday evenings after work to socialize and encourage collaborative solutions. These relationships and our collective ability to ask and answer (or get answers for) important questions represented one of the most important drivers for the expansion and continuation of the project. While analysts cannot always choose to enter a project with a highly functional team, the first two authors appreciated that their efforts on this project benefited tremendously from their acceptance into a highly effective and functional team, and that this represented an important advantage. Everyone worked collaboratively at all levels and viewed all interactions as opportunities to learn, and answer questions that others might raise about the modeling. The group recognized the process is the product of the collaboration.

One of the important and ongoing communication challenges relates to the need to negotiate and adapt to different institutional and professional cultures and communication styles. For example, some of the collaborators expected information in the form of very brief presentations and short written pieces that favored brevity and simplicity. This contrasted with the expectations of other collaborators who sought to provide comprehensive and rigorous reviews of scientific information and discussions of complexity that would support model development. The different styles led to important compromises in the overall products of the project. For example, while some collaborators preferred to complete full articles for submission for peer review, others wanted to know the bottom line, act on the insights, and move on with less concern about publication. The first manuscript from the collaboration centered on enumerating the complete list of the actual decisions and their interactions that national policymakers would face, which we achieved using the decision tree shown in Fig. 4.⁽¹⁵⁾ In developing this information, we recognized and clearly identified the different starting points for individual nations and this led us to decide that we needed

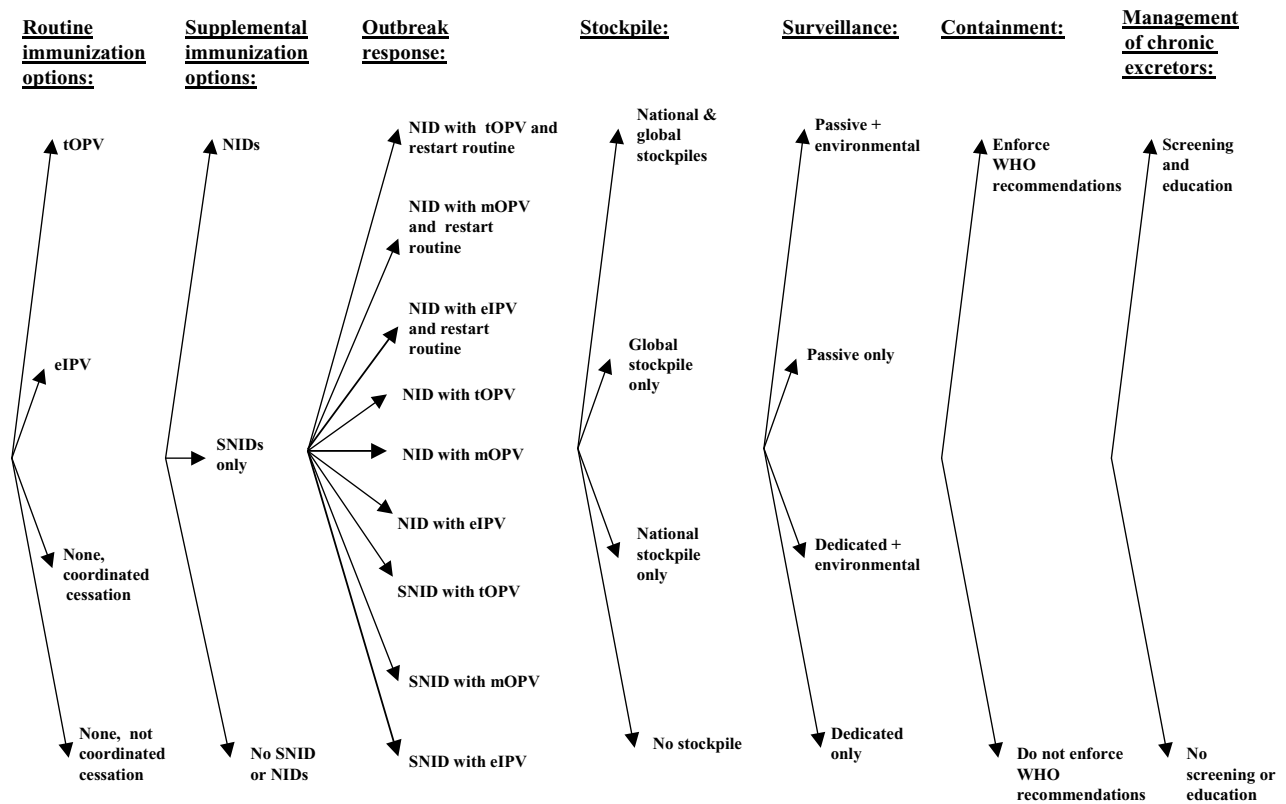


Fig. 4. Major decision options for all countries—first five years after certification of the world as free of wild polioviruses. Each branch represents a decision option for a given decision category (source: Reference 15).

to stratify the world to capture some of the wide range of variability in the decisionmaking perspectives and sources of risk. From the analytical perspective, we clearly saw the differences in starting points and that countries might prefer different strategies depending on their risks and available resources. In particular, we knew that developed countries like the United States would probably continue routine IPV use into the foreseeable future, even with the global eradication of wild polioviruses. At the same time, competing demands for resources would reasonably lead developing countries to choose to stop polio vaccinations completely as soon as safely possible after global eradication. Our appreciation of the importance of characterizing variability and uncertainty in the risks led us to find effective ways to discuss the many possible futures.

2.4. Requirement 4: Stay Organized, Focused on Quality, and Flexible

“You must do the things you think you cannot do.”
Eleanor Roosevelt

“Delay is preferable to error.”

Thomas Jefferson

Once we identified the full set of decision options that we would include, we turned our attention to refining our dynamic disease model and the other components of the overall model.^(17,21,22) Remarkably, in spite of all of the historical outbreaks that occurred with polio, no dynamic disease models existed that could appropriately account for the subtleties in infectivity for people with different vaccination/infection history and realistic outbreak response. Although we started with a relatively simple susceptible-infected-removed (SIR) model, the model quickly grew in complexity. For example, we recognized that the underlying population immunity structure reflected a mixture of individuals fully susceptible to disease and those partially infectible, but resistant to disease. We recognized important differences between people who had recent infection with the wild virus or vaccine, those with historic live virus infection, and those protected by IPV vaccination. Fig. 5 shows a simplified schematic for the first age group (with newborns entering the model, but

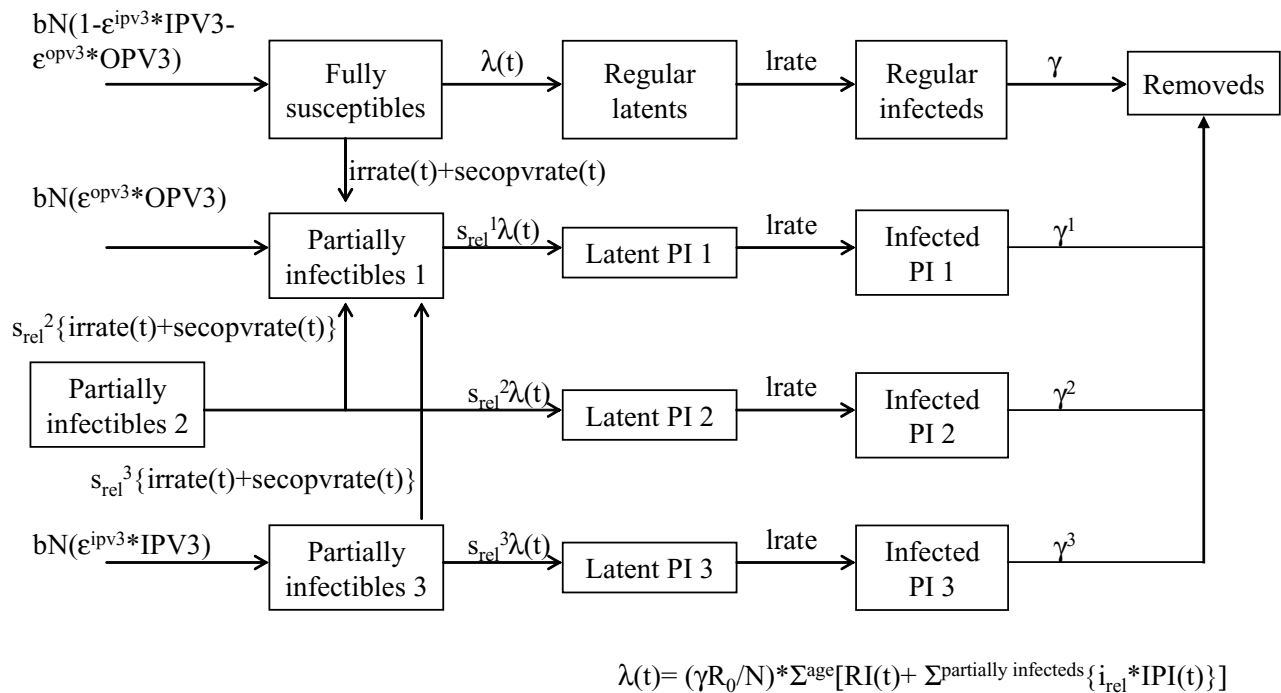


Fig. 5. Schematic of dynamic disease model components for the first of 25 age groups extending on the basic SIR model though inclusion of three different groups with partial immunity (due to prior recent or historical vaccination or exposure to wild poliovirus).⁽¹⁷⁾

not showing the similar schematic for the second age group or the arrows connecting them). We ultimately decided to model 25 separate age groups with different initial immunity profiles to capture the differences in historical vaccination and to maintain our ability to include different target population groups for modeling a wide range of potential outbreak response strategies. We went through several iterations on the model and benefited from the opportunity to apply the model to data from real outbreaks that helped us learn about how the model performed on some retrospective cases and identify critical model parameters. In the context of informing future policies, we faced the challenge of trying to characterize the impacts of potential outbreaks prospectively. Given uncertainty about the actual conditions, we made a significant number of assumptions and modeled the uncertainty about the many possible futures. We developed a hypothetical potential outbreak and used it to demonstrate the expected impacts of different strategies for responding to that outbreak.⁽²¹⁾ Building on this work, we performed a more comprehensive analysis of response scenarios in different settings that helped policymakers identify reducing the delay in outbreak response as a major priority.⁽²³⁾ We emphasize that once specific information about any real outbreak becomes

available the model can and should use that information to provide a more informed estimate (e.g., the model uses as a starting point characteristics of the different serotypes of polioviruses “averaged” for types 1, 2, and 3, but clearly once we know the type of virus responsible for any given outbreak the model should use inputs specific for that type). In this context, we believe that early recognition of and investment in methods for performing uncertainty and sensitivity analysis for dynamic models⁽²⁴⁾ will prove useful. They would answer requests from decisionmakers who want more than point estimates and to demonstrate the existence and impacts of uncertainties in the model that we might otherwise miss.

The important insights from the model came from its ability to demonstrate the potential impact of different scenarios. For example, we used the model to demonstrate that, because of the risks of cVDPV outbreaks, sustained eradication of circulating live polioviruses would require eradication of OPV as soon as possible after the confirmed eradication of wild polioviruses. We also emphasized that policymakers should prepare the world for the relatively high probability of at least one outbreak occurring after eradication, and that they must prepare to respond to such an outbreak and not consider such an event as a signal of

the failure of global eradication. Our model included key placeholders for a stockpile and response strategy, and we emphasized the importance of planning and preparation, which helped to contribute to efforts to establish a global stockpile. We are now also at the point that the collaboration has produced the “full” model that we can use to explore the main policy options and characterize their risks, costs, and benefits.

2.5. Requirement 5: Keep Learning and Asking Good Questions

“Can anybody remember when the times were not hard and money not scarce?”

Ralph Waldo Emerson

“Though analogy is often misleading, it is the least misleading thing that we have.”

Samuel Butler

Throughout the effort, all collaborators worked to ask good questions, recognizing that the important questions change and iteration occurs. As we gained understanding and identified key gaps in knowledge, the modeling process needed to accommodate our conceptual evolution. While it may seem ideal for a project like this one to closely follow a static plan, the reality is that the process itself needed to be dynamic and we truly needed to learn as we went. In some cases, review of our assumptions led us to refocus, reframe, and/or adapt the model to better capture new information.

Overall, this collaboration led to a number of lessons learned. First, all members of the team must commit to a long-term relationship to evolve within the context of an ongoing program, something that is not typical for economic analysts. Second, the analysts must commit to educating the subject area experts and to accepting and seeking education from the experts in a way that embraces changes. Third, the collaborators must commit to full transparency in developing and modifying assumptions as well as models and commit to sharing key information as it becomes available. Finally, to influence real decisions, the collaborators must commit to ensuring all programmatically important insights get translated into formats readily accessible to the multiple audiences the policymakers seek to inform and influence. All of this takes time to develop.

As we look to the future, we see several tests of the model and the process that will ultimately determine its fate. We hope that as long as we continue to ask good questions we will be able to provide valu-

able insights and contributions. Our collaboration has led us to a greater appreciation of the value of process (iterative, collaborative, and evolving) as well as product (the actual model w/full schematic, quantified risk assessments, etc.) and the continual interaction between the two. Importantly, our work has created a “platform” to engage policymakers and scientists at all levels. Some of the biggest challenges that we anticipate will come from the need to provide answers to key questions in ways that meet the needs of different audiences and reflects the best available scientific evidence. This will require effective communication, but also recognition that the questions asked will change. While we talk about variability, national leaders talk about the options as they see them. Our discussions about the future and highly uncertain risks (e.g., bioterrorism) reveal very different perceptions of the risks and preferences for managing uncertainties. Successful elimination of paralytic polio will require the elimination of OPV, yet coordinating the process of cessation will mean obtaining global agreement with a policy and compliance with its implementation. We see many opportunities for further use and iteration of our model, and the modeling process continues to respond to new demands.

Coming full circle to the retrospective analysis that started this collaboration, we find a strong analytical case for economic analysts to use dynamic models in costeffectiveness and for policymakers to rely on dynamic models and processes instead of static ones. In highlighting the changes that occur in the costeffectiveness of vaccines over the course of their lifecycles, we believe that the polio experience provides a wealth of lessons, most notably the need to appreciate the major changes that occur over time.⁽⁵⁾

3. CONCLUSIONS

Analysts can contribute significantly to real policy decisions, but only if they commit to a process for doing so, work effectively with a team of others with required expertise, and recognize the dynamic nature of both policy and science. We hope that providing a review of the requirements for our success (at least up to this point) in developing a model and process to support consideration of policy options, we have provided some useful insights for other modelers and similar collaborative processes. We recognize that a model only helps when people use it, and in this regard we aspire to create and maintain a living model that will support real high-level policies as world leaders

continue to face the challenges of managing the global risks of polio over time.

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